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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

| EXAMINER | |
|---|---|
| MORRIS, PATRICIA L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1625 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/782,376 | BONIFACIO ET AL. | |
| | Examiner | Art Unit | |
| | Patricia L. Morris | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *27,28,37-42 and 50-92* is/are pending in the application.

4a) Of the above claim(s) *37-42,51-81,83,84 and 92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,82 and 85-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 27, 28, 82 and 85-91 are under consideration in this application.

Claims 37-42, 51-81, 83, 84 and 92 remain held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

### *Election/Restrictions*

The restriction requirement is deemed sound and proper and is hereby made FINAL.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 27, 28, 82 and 85-91 are rejected under 35 U.S.C. 102(a), (b) and/or (e) as being anticipated by Sartani et al. and Testa et al. for the reasons set forth in the previous Office action.

Again, Sartani et al. and Testa et al. disclose the instant compound and compositions. Note page 189 of Testa et al., example 3 of Sartani et al.. Hence, the instant compound is deemed to be anticipated therefrom.

Applicants appear to couch there arguments with regards to the process of making, however, applicants' claims are drawn to **compounds.**

Contra to applicants' arguments in the record, a novel chemical product is identified first by its "chemical nature", ie., elemental and atom content. It is a well known fact that many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (see US Pharmacopia #23) and more than half the pharmaceuticals exhibit polymorphism or as more or less amorphous products (see the abstract of Doelker). Polymorphs are different crystalline forms of the **same pure substance** in which the molecules have different arrangements and/or different conformations of the molecules. Brittain concluded this per ponderous of conventional nature in the text book "Polymorphism in Pharmaceutical Solids" on page 2 that "*in the strictest sense, polymorphs are different crystalline forms of the* **same pure substance** *in which the molecules have different arrangements and/or different conformations of the molecules".*

Applicants merely allege that the prior art compounds are not the same as the crystalline compounds since they fail to show the same powder X-ray diffraction patterns. However, applicants have failed to provide any objective evidence, *i.e* crystal powder X-ray diffraction patterns of the instant compounds *vis-à-vis* the prior art compounds at the same radiation parameters. Mere allegations by applicants do not take the place of objective evidence showing side-by-side X-ray diffraction pattern comparisons at the **same** radiation parameters of the claimed compound and the compounds of the prior art.

X-ray diffraction pattern **alone** does not demarcate the identity of two products. It is well recognized in the crystalline solid art that sometimes the difference in X-ray diffraction pattern is very minor and must be carefully evaluated before a definitive conclusion is reached. See US

Pharmacopia of record. Further, Davidovich et al. on page 16, states that changes in powder X-ray diffraction often resulted from experimental artifacts rather than polymorphism and that most of these changes were due to particle size/morphology, sample holder/preparation and instrument geometry. Note figure 4.21 on page 118 of Bernstein wherein the same compound shows two different X-ray patterns. Page 272 of Bernstein shows that two identical X-ray patterns, but one is the chemical compound pigment Yellow 14, wherein R is $CH_3$, while the other is the pigment Yellow 63, R is Cl. Thus, this is an example of identical X-ray displayed by different compounds. The figure on page 273 showed that two X-ray diffraction patterns collected on crystals and recrystals after melting. Although, there are new peaks, the authors concluded that "it may not be a pure modification", *i.e.,* not a true polymorph. Caira recites several cases of "vanishing" polymorphs. Note page 165 therein.

The newly added references are supplied to as state-of-the-art evidence rebutting applicants' arguments in the instant response.

***Claim Rejections - 35 USC ∋ 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 28, 82 and 85-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Sartani et al. and Testa et al. in view of Haleblian et al., , Brittain et al., Taday et al, US Pharmacopia, Muzaffar et al, Jain et al. and Concise Encyclopedia Chemistry for the reasons set forth in the previous Office action.

Again, Sartani et al. and Testa et al. teach the crystal forms of the instant compound and as well as the pharmaceutical compositions. Note column 7, lines 42-47, of Sartani et al. Haleblian et al., Muzaffar et al., Jain et al., Taday et al. and Brittain et al. teach that compounds exist as polymorphs. Chemical & Engineering News, Muzaffar et al., US Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different polymorphic forms. No unexpected or unobvious properties are noted.

Changing the form, purity or other physical characteristic of an old product does not render the new form patentable where the difference in form, purity or characteristic is inherent or rendered obvious by the prior art. In re Cofer 148 USPQ 268. Mere difference in physical property is a well known conventional variation for the same pure substance (see Brittain, p. 1-2) is prima facie obvious.

It is well recognized in the pharmaceutical field that many solids exhibit polymorphism which is the innate nature of the particular drug. See, for example, US Pharmacopia. Contra to applicants' arguments in the instant response, the prior art of record clearly shows that lansoprazole exhibit polymorphism. It is also well recognized in the art that the different polymorphs will display different physical properties such as X-ray diffraction, melting point, etc., (see Jain et al. or page 33 of Chemical Engineering News). As clearly stated by Brittain (p. 1-2) supra, as well as set forth in In re Cofer 148 USPQ 268, ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant compounds are drawn to the ***same pure substance*** as the prior art that only have *different arrangements and/or different conformations of the molecule.* A mere difference in physical property is a well known conventional variation for the same pure substance is prima facie obvious.

Applicants have failed to show any unobvious properties of the instant compound *vis-à-vis* the prior art compounds. It is apparent that applicants need a reference to show that a **showing of unobvious properties is necessary.** Note Brittain et al. (already of record), page 185, where it is stated: **"In 1990 Bryn and Pfeiffer found more than 350 patents on crystal forms granted on the basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, etc.,". Applicants have failed to show any advantage for the instant polymorphs.**

***Claim Rejections - 35 USC ∋ 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Again, there is a lack of description as to whether the pharmaceutical carriers are able to maintain the compound in the polymorphic form claimed. Processing a compound into a pharmaceutical composition could create a different polymorph than the polymorphs being claims or even back to the compound itself. See pages 912-913 of Habeblian or page 33 of Wall et al. Jain et al., pages 322-326 teach that manufacturing processes affect polymorphs. Taday et al. on page 831, teach "..Once in the desired crystalline form, the polymorphic state may be changed by incorrect storage or even during tablet preparation". Doelker et al. Abstract (English translation of the French reference now provided), "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or dosage form." The specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or infrared spectrum data. The X-ray diffraction and Infrared spectrum data in the specification only pertains to the compounds rather than the compositions being claimed. The specification has also not described how the polymorphic forms and compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment of type II diabetes.

Contra to applicants' assertions in the instant response, applicants have failed to provide any objective evidence that the instant polymorph is indeed maintained in the compositions. Applicants present some general references attempting to show that the instant polymorph in the composition is stable. However, the references do not pertain to the particular polymorph. Applicants have provided **no objective evidence** that the instant polymorph will not be identical to the prior art compounds because ***"when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"*** **(see Jain p. 316).** It is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if one is in possession of a particular crystalline form, no predictability can be found that such forms will prevail in pharmaceutical compositions. See Chemical & Engineering News.

Applicants merely allege that the examiner has failed to show why the compositions are not enabled. Applicants were given numerous references showing that the pharmaceutical formulation field is well aware that polymorphs when being formulated into compositions may undergo transformation thus, the particular form may not be the same form after processing, compressing, etc. (see Chemical & Engineering News, pages 34-35). Therefore, in the absence of any description or factual evidence, how a crystalline form can be maintained in a composition to minimize transformation, no assumption can be made that the meta-stable polymorph will be maintained upon compression, tableting, etc.

Chemical & Engineering News discloses that formulation of drugs or pharmaceuticals in its metastable forms, for example, one polymorph, is highly unpredictable. The metastable

forms will disappear and change into the most thermodynamically stable form. The specification lacks description of how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared spectra and X-ray diffraction being claimed. Disclosure of X-ray diffraction patterns for pharmaceutical compositions comprising the polymorphic forms are lacking in the specification. The X-ray diffraction patterns in figure 1 only supports the polymorphic forms of the compounds and not the pharmaceutical compositions. Jain et al.., p 322-326, recite the manufacturing processes that affect polymorphs. Otsuka et al. On page 852 states « in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process".

The specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Applicants are referred to In re Fouche, 169 USPQ 429 CCPA 1971, MPEP 716.02(b).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

***The nature of the invention***

The nature of the invention is the preparation of novel polymorphic forms of the instant compound and compositions.

***State of the Prior Art***

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. (See Chemical Engineering News, page 32). Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. Additionally, solids may form solvates. Polymorphs tend to convert from less stable to more stable forms. (See Chemical Engineering News, page 32). No method exists to predict the polymorphs of a solid compound with any significant certainty. In drug design, it is best work with the most stable polymorph, because it will not covert any further, however, the most stable polymorph usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, choosing to work instead with the less stable forms first, also known as the metastable forms. Polymorphs can convert from one form to another during the manufacturing process of a pharmaceutical drug. See Chemical Engineering News. Page 33, which will changed the pharmacological affects of the drug. This is why it is important to monitor the polymorph during manufacture of the drug to see if it persists during manufacture.

***The amount of direction or guidance and the presence or absence of working examples***

Figures 1-4 of the specification only disclose the X-ray diffraction pattern and infrared spectra of compounds of particular forms rather than the compositions being claimed in terms of the specific X-ray diffraction patterns. Polymorphs often change into other polymorphs during

drug manufacture (See Chemical Engineering News) into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the pharmaceutical compositions. Further, in the aqueous phase, all physical forms are amorphous (see Ulicky). Also, note page 316 of Jain et al. where it is stated "when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"

Further, the specification has also not described how all the crystalline forms and composition being claimed will be maintained and prevented from converting to other forms when used in the treatment of diabetes. It is well recognized in the art that the compound is given to the subject in a physiological environment, *i.e.,* administered. As discussed supra, there is no description or enabling support that the instant polymorph will be in its physical form and biological activity results from the particular form instead of the solution state of the compound.

***The breadth of the claims***

The breadth of the claims are drawn to the specific polymorph forms and in addition to the pharmaceutical compositions.

***The quantity of experimentation needed***

The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to the pharmaceuticals compositions being claimed and verifying that they have the specific X-ray diffraction patterns being claimed which are not disclosed in the specification.

In terms of the 8 Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of

unpredictability in the art of the invention, and the poor amount of direction provided by applicants. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patricia L. Morris
Primary Examiner
Art Unit 1625

plm
June 5, 2007